

## **REMARKS**

### **I. Claim amendments**

The Office Action Summary (PTOL-326) indicates that the final Office Action is responsive to the Amendment filed 10 February 2009. However, Applicants submitted a supplemental Amendment on 11 February 2009 which, in view of the Office Action Summary, may not have been entered and considered. Therefore, by this communication, Applicants have re-introduced the same amendment to claim 17 which had previously been introduced by the supplemental Amendment, filed 11 February 2009.

In addition, claim 1 has been amended to recite that the nano-crystalline particles prepared in accordance with the claimed process have a mean particle size of from 10 to 200 nm. Support is found on page 4 of the specification at lines 28-31. Claim 2 has been canceled in view of amended claim 1.

Applicants submit that no new matter has been introduced by the claim amendments.

### **II. Claim rejection – 35 U.S.C. §112**

Claim 4 is rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. The Examiner alleges that the expression “the aqueous medium”, as recited in claim 4 at line 2, lacks antecedent basis.

The preamble of claim 1 provides that the claimed process is directed to the preparation of a dispersion of nano-crystalline particles in an aqueous medium. In accordance with process step (a) of claim 1, the aqueous medium is formed by the combination of a first solution and an aqueous phase. Claim 4 is directly dependent on claim 1. Claim 4 provides that the concentration of the substantially water-insoluble substance in the aqueous medium following step (a) is 10mM or less.

In view of the foregoing, Applicants respectfully submit that the preamble of claim 1 provides antecedent basis for the expression “the aqueous medium” as recited by claim 4. Withdrawal of the §112 rejection is requested.

### **III. Claim rejections – 35 U.S.C. §103**

#### **a. Kipp + Lüddecke**

Claims 1-10 and 12-20 are rejected under 35 U.S.C. §103(a) as being unpatentable in view of US 6,607,784 to Kipp et al. ("Kipp") in view of US 5,895,659 to Lüddecke et al. (Lüddecke).

In accordance with the claimed process, a first solution and an aqueous phase are combined under rapid mixing to form a dispersion of amorphous particles (p. 9, lines 29-30). Without wishing to be bound by theory, it is thought that the formation of the initial suspension of amorphous particles promotes the subsequent formation of a uniform dispersion of nanocrystalline particles during the subsequent sonication. As demonstrated by the Examples 1-4, 6 and 7, nanocrystalline particles having a mean particle size of 10 to 200 nm are obtained with the claimed process.

On page 3 of the Office action, the Examiner acknowledges that Kipp does not explicitly teach either a mean particle size of from 10-280 nm or rapid mixing, e.g., less than 30 seconds. For this purpose, the Examiner relies on Lüddecke.

#### **1. Claimed particle size of from 10 to 200 nm**

Kipp discloses three process categories for preparing submicron suspensions. These categories are described at column 5, lines 4-35, and again at column 10, lines 3-67. In the first process category, the organic compound in the presuspension takes an amorphous form, a semi-crystalline form or a supercooled liquid form (col. 5, lines 4-8; col. 10, lines 8-9). In the second process category, the organic compound in the presuspension is in a crystalline form (col. 5, lines 12-14; col. 11, 34-35). In the third process category, the presuspension is in a crystalline form that is friable (col. 5, lines 22-24; col. 11, lines 46-47). Each of the first, second and third process categories can be further divided into subcategories, Method A and B, which are illustrated in Figures 1 and 2 and described in the disclosure beginning at column 6, lines 33, to column 8, line 10.

It is evident, therefore, that Kipp's process category one is closest to the claimed invention when the presuspension takes an amorphous form but not when the presuspension of process category one takes a semi-crystalline form or a supercooled form which is distinguishable from the claimed invention. With specific regard to the size of particles prepared

in accordance with process category one, Kipp discloses the range “from about 400 nm to about 2  $\mu$ m” (col. 5, line 11) which is clearly distinguishable from the claimed range of 10 to 200 nm.

To remove any ambiguity from the record, the Examiner’s attention is directed to the following disclosure by Kipp that Applicant more fully appreciated after a subsequent consideration of the reference. Specifically, Table 1 (Method B) at column 9 discloses particles having an average particle diameter of 0.178-0.194 (microns). However, there is no disclosure of the method, i.e., process category one, two or three, by which these particles were made.

According to Kipp, process categories one and two share a similar feature wherein the organic compound after the energy-addition step is in a crystalline form having an average effective particle size essentially the same as that of the presuspension (col. 5, lines 8-11 and 14-18). This is distinguishable from the third process category wherein the organic compound after the energy-addition step is in a crystalline form having an average particle smaller than the crystals of the presuspension (col. 5, lines 27-29). As reported in Table 1, the average particle diameter (microns) of the particles prepared in accordance with Method B is essentially the same as that of the presuspension. Therefore, based on the disclosure provided by Kipp, the particles prepared by Method B as reported in Table 1 may have been prepared by either process category one or two but probably not by process category three which is characterized by an average particle size that is smaller than the crystals of the presuspension (See Table 1, Methods A).

In any event, Kipp is silent with regard to the process by which the particles reported in Table 1, Method B were prepared and whether the presuspension was in an amorphous form, a semi-crystalline form or a supercooled liquid form. As previously mentioned, Kipp’s process category one is closest to the claimed invention when the presuspension takes an amorphous form but not when the presuspension of process category one takes a semi-crystalline form or a supercooled form which is distinguishable from the claimed invention.

## 2. Lack of motivation to combine references

Furthermore, Applicants respectfully submit that there is no motivation to combine Kipp with Lüddecke. And if there were any motivation - which Applicants do not admit, it is submitted that Lüddecke fails to overcome the failure of Kipp to suggest the rapid mixing step of the claimed invention.

Firstly, the express purpose of Lüddecke is to provide finely dispersed carotenoid and retinoid suspensions in which it is possible to dispense with a protective colloid (col. 2, 11-14). As background at column 1, lines 41-56, Lüddecke discusses EP-B-0 065 193 which describes a process for preparing finely dispersed carotenoids and retinoid products in powder form. US 4,522,743 to Horn et al. (the "743 patent") belongs to the same patent family as EP-B-0 065 193. The '743 patent discloses the following colloids that can be used:

Examples of swellable colloids used are gelatin, starch, dextrin, pectin, gum arabic, casein, caseinate and mixtures of these. However, polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose and alginates may also be employed. For further details, reference may be made to R. A. Morton, Fat Soluble Vitamins, Intern. Encyclopedia of Food and Nutrition, Volume 9, Pergamon Press 1970, pages 128-131. To increase the mechanical stability of the end product, it is advantageous to add to the colloid a plasticizer such as a sugar or sugar alcohol, eg. sucrose, glucose, lactose, invert sugar, sorbitol, mannitol or glycerol.

(See '743 patent at col. 3, lines 27-39).

Therefore, to fulfill the express purpose of Lüddecke, i.e., to dispense with a protective colloid, Lüddecke cannot be combined with a reference that teaches the use of a colloid.

Specifically, the primary reference to Kipp teaches the use of a colloid which represents an incompatible teaching with Lüddecke. Regardless whether it be process category one, two or three or subcategory Method A or B, Kipp teaches that an organic compound is dissolved in a first solvent or mixture of solvents. Examples of that first solvent include polyvinylpyrrolidone and polypropylene alginate (col. 6, lines 12 and 28). Polyvinylpyrrolidone and alginates are examples of colloids as defined by the '743 patent which are to be avoided in accordance with the express purpose of Lüddecke, i.e., to dispense with a protective colloid. Furthermore, in accordance with Method A, one or more surfactants is added to the second aqueous phase (col. 6, lines 40-44). And in accordance with Method B, one or more surfactants is also added to the first solution (col. 8, lines 5-10). Examples of such surfactants include polyvinyl alcohol (col. 7, lines 7-8), polyvinylpyrrolidone (col. 7, line 8) and methylcellulose (col. 7, line 5). Each of these surfactants is expressly defined by the '743 patent as a colloid to be avoided in accordance with the express purpose of Lüddecke, i.e., to dispense with a protective colloid.

Applicant submits, therefore, that the combination of Kipp and Lüddecke defeats Lüddecke's express object of providing a process for preparing finely dispersed carotenoid or retinoid suspension in the absence of protective colloid (See claim 1 of Lüddecke).

Secondly, notwithstanding any general disclosure by Kipp regarding the rate of mixing of solutions, e.g., at column 5, line 54, and column 7, lines 30-34, Kipp teaches against rapid mixing as contemplated by the claimed invention, e.g., less than 30 seconds. As demonstrated by all of Kipp's working examples, there is not even a scintilla of any suggestion of rapid mixing:

- Example 1 - "slowly (1-3mL/min)" at col. 11, line 36
- Example 2 - "slowly (1-3mL/min)" at col. 12, line 39
- Example 3 - "slowly (1-3mL/min)" at col. 13, line 17
- Example 4 - "slowly (1-3mL/min)" at col. 13, line 60
- Example 5 - pump was set at 1 mL/min (col. 14, line 27)
- Example 6 - "dripped at 0.1 mL/min" at col. 14, lines 67
- Example 7 - addition rate of 0.1 mL/min at col. 15, line 20
- Example 8 - addition rate of 0.1 mL/min at col. 15, line 61
- Example 9 - addition rate of 2.5 mL/min at col. 17, line 52
- Example 10 - "dripped at 2.5 mL/min" at col 18, line 61
- Example 11 - "slowly added (approximately 0.8 mL mL/min)

Therefore, Kipp clearly teaches against the disclosure of rapid mixing within less than 10 seconds as disclosed by Lüddecke. As such, there is an absence of motivation to combine these references.

Finally, Lüddecke does not disclose or suggest the claimed process step of rapidly mixing a first solution comprising a substantially water-insoluble substance in a water-miscible organic solvent with an aqueous phase. Rather, Lüddecke discloses mixing a carotenoid or retinoid with a water-miscible solvent within less than 10 seconds to form a first solution. But there is no disclosure or suggestion of rapidly mixing that first solution with an aqueous phase as claimed. Example 1 of Lüddecke discloses that the first solution after rapid mixing (0.35 sec) is metered at a rate of about 30 l/h into a second chamber and mixed with water. Again, there is no disclosure or suggestion of rapid mixing with an aqueous phase as claimed.

In conclusion, Applicants submit that there is no motivation to combine Lüddecke with Kipp:

- the use of a colloid by Kipp as a first solvent and surfactant, e.g., polyvinylpyrrolidone, alginates, methylcellulose and polyvinyl alcohol, is incompatible with Lüddecke;
- notwithstanding any general disclosure by Kipp regarding the rate of mixing of solutions, the working examples evidence a teaching by Kipp against rapid mixing as contemplated by the claimed invention; and
- Lüddecke fails to disclose or suggest the claimed step of rapidly mixing a first solution with an aqueous phase.

Therefore, the combination of Kipp and Lüddecke is improper and, in any event, does not suggest the claimed invention. For all of the foregoing reasons, a *prima facie* case of obviousness has not been established. Withdrawal of the §103 rejection based on the combination of Kipp and Lüddecke is requested.

b. Lindrund + Lüddecke

In contrast to the claimed invention, Lindrud does not disclose a step for forming a dispersion of amorphous particles. Rather, Lindrud is directed to *a continuous crystallization process* (p. 2, lines 24-28) which involves the formation of a crystallization slurry (p. 5, lines 9-11). Lindrud applies ultrasound energy to the continuous crystallization process to form crystals having a diameter of less than one micron (Abstract, Examples 1 and 2).

The Examiner appears to agree since the previous rejections under 35 U.S.C. §§102 and 103 in view Lindrud were withdrawn. The Examiner's reliance on any disclosure of rapid mixing by Lüddecke is misplaced since the combination with Lüddecke fails to alter the fact that Lindrud is directed to a continuous crystallization process. Again, the Examiner appears to agree since at page 5 of the Office Action, the Examiner states that Example 1 of Lindrud shows a temperature of 2°C "*throughout the crystallization*". Lindrud is silent whether or not an amorphous or crystalline suspension is formed. However, this is irrelevant since Lindrud cannot be modified without destroying its intended purpose and function, i.e., a continuous crystallization process

Finally, Applicants repeat that Lüddecke does not disclose or suggest the claimed process step of rapidly mixing a first solution comprising a substantially water-insoluble substance in a water-miscible organic solvent with an aqueous phase. Rather, Lüddecke discloses mixing a

carotenoid or retinoid with a water-miscible solvent within less than 10 seconds to form a first solution. But there is no disclosure or suggestion of rapidly mixing that first solution with an aqueous phase as claimed.

In conclusion, Applicants submit that there is no motivation to modify Lindrund to arrive at the claimed invention without destroying the intended purpose and function of Lindrund, i.e., a continuous crystallization process. Furthermore, Lüddecke fails to disclose or suggest the claimed step of rapidly mixing a first solution with an aqueous phase. Therefore, the combination of Kipp and Lüddecke, although improper, does not suggest the claimed invention.

For all of the foregoing reasons, a *prima facie* case of obviousness has not been established. Withdrawal of the §103 rejection based on the combination of Lindrund and Lüddecke is requested.

### **CONCLUSION**

For all of the foregoing reasons, Applicants submit that claims 1, 3-10 and 12-20 are in condition for allowance which action is earnestly solicited.

Any fee due in connection with this response should be charged to Deposit Account No. 23-1703.

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Respectfully submitted,

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